Co-evolutionary and systemic study on the evolution of emerging stem cell-based therapies

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Newly emerging therapeutic technologies have the potential to reconfigure the understanding, diagnosis, and treatment of diseases, and, consequently, to impact human health. This study integrates co-evolutionary and system-oriented perspectives to investigate factors influencing the way emerging therapies evolve in their attempt to become established medical practices. We examined the case of the use of induced pluripotent stem (iPS) cell-based therapies for age-related macular degeneration (AMD) disease. Cell therapy evolution is explored by considering their constitutive components, namely disease, biomedical technologies, and clinical practices, and observing the changes experienced by their underlying knowledge structures. We adopted a mixed methods approach that simultaneously uses publication, patent, and clinical trial data. Our results highlight the significance of the diversity of technological possibilities, the role of subjective issues in the selection of directions of search, the complementary nature between established and emerging therapies, and the tight product-process interdependencies. This study contributes to an understanding of the difficulties encountered during the emergence of new cell therapies, and the ways in which such difficulties can be circumvented to establish effective and safe cell-based clinical practices.

1. Introduction

Newly emerging technologies signify radical novelty, relatively faster growth, coherence, prominent market and economic impact, and uncertainty and ambiguity (Rotolo et al., 2015; Wagner et al., 2011). Although technological emergence is a common phenomenon in the economic system (Kauffman and Macready, 1995), it is highly temporal and spatial in nature. The locus of intense technological creation has shifted across knowledge domains over time, from information and communications technology and biotechnology to nanotechnology (Islam and Miyazaki, 2010). Each time, waves of technological change and transformation are created and diffused across industries and economies (Lipsey et al., 2005; Perez, 2010). The field of life sciences, and biomedicine in particular, is emerging as one of the most promising "hot spots" of innovation discontinuity (Grinin et al., 2017; Sharp and Langer, 2011). Some examples of novel biomedical technologies expected to impact human health and well-being are cancer immunotherapies, RNA-based therapies, gene therapies, precision medicine, and cell therapies (NRC, 2014).

Medical knowledge changes, evolves, and transforms throughout its translation into safe and effective therapies for the cure, treatment, and prevention of diseases (Mina et al., 2007). The examination of the patterns of dynamics and change in newly emerging technologies is of great interest for policy makers and researchers as it provides key insights into the future pathways of growth (Coccia and Wang, 2015; Larédo et al., 2015; Robinson et al., 2013). The complex, uncertain, and open-ended nature of medical knowledge (Gelijns et al., 2001; Metcalfe et al., 2005) makes it difficult to study the future of novel technologies. Faced with these difficulties, recent studies have proposed more broad-encompassing approaches for assessing the progress of medical knowledge. Two main research streams stand out in the literature, namely co-evolutionary and systems-oriented perspectives.

Building on a co-evolutionary approach, studies have conceptualized the progress of medical knowledge from multiple pathways and their interactions, including disease (demand issues), biomedical technologies (technological competencies), and clinical procedures and practices (supply issues) (Morlacchi and Nelson, 2011; Nelson et al., 2011; Petersen et al., 2016). Other studies have examined the evolution of medical knowledge from a systems perspective, such as Consoli and Ramlogan (2008)'s "Health Innovation Systems" and the different applications of technological innovation systems approaches (Kukk et al., 2015; Kukk et al., 2016; Musiolik et al., 2012; Wirth and Markard, 2011). Whereas the former approach focuses on the different complementary domains involved in the development of novel technologies and their interactions, the latter

emphasizes the components making up particular biomedical innovation systems, including the technologies, actors, institutions, and networks. Despite the high complementarity between both research streams, studies integrating both approaches into a single framework have not been reported yet.

Through the integration of co-evolutionary and systems-oriented perspectives, this study aimed to examine the factors influencing the evolution of emerging medical knowledge into potential therapies for patients. We dissected the emergence of novel therapies into three constitutive components, namely disease, biomedical technologies, and clinical procedures and practices (Morlacchi and Nelson, 2011; Nelson et al., 2011; Petersen et al., 2016). By visualizing these components as complementary technological innovation system (TIS), we analyzed them in terms of the changes experienced by the underlying knowledge structures. We operationalized knowledge structures using several network approaches. We use a comprehensive mixed-methods approach that includes the simultaneous use of scientific, technological and clinical data, supported by interviews with key experts as well as the review of the "grey" literature, such as market and technical reports. Our empirical analysis is based on the case of cell therapies, i.e. the transplantation of any type of cells to replace or repair tissues or organs. We focused on cell therapies based on induced pluripotent stem (iPS) cells, the latest stem cell species, used for the treatment of age-related macular degeneration (AMD), a degenerative disease affecting the back of the retina.

We selected this case study for three reasons. First, iPS cells are emerging technologies, whose groundbreaking nature was recognized in 2012 through the conferral of the Nobel Prize in Physiology or Medicine to its discoverer, Prof. Shinya Yamanaka of Kyoto University. Second, AMD is not only a globally unmet health problem, but it is also the first condition for which the use of iPS cells has reached a clinical trial stage (i.e., application on actual human patients), even if it is in an exploratory stage. Third, despite their potential therapeutic and commercial impacts, cell therapies are still highly underrepresented in the innovation literature, mostly focusing on ethical and regulatory concerns. Owing to the diversity of field of life sciences (Styhre, 2015), additional case studies can help to further clarify the commonalities and differences across various sectors and technologies (Consoli et al., 2016).

Methodologically speaking, this study considers not only multiple dimensions but also the simultaneous use of scientific, technological and clinical trial data when studying the evolution of newly emerging medical knowledge. We contribute to the study of emerging technologies by revealing the factors influencing the evolution of novel cell therapy knowledge into clinical practices. Our results highlight the significance of the diversity of technological possibilities, the role of subjective issues in the selection of directions of search, the complementary nature between established and emerging therapies, and the tight product-process interdependencies. We also demonstrate the high dependence of the evolution of therapies on the characteristics of the disease, the targeted organs, and the clinical procedures. Policy makers should be aware of such aspects, as they can provide helpful avenues for the translation of new cell therapies into effective and safe clinical practices.

This paper is structured as follows. Section 2 presents an overview of the relevant literature and the conceptual framework used in this paper. Section 3 briefly describes the case under study, i.e. iPS cell-based therapies for AMD disease, and presents the research design used in this study. Section 4 continues with the description of analysis results on the knowledge structures underlying iPS cell technologies, AMD disease, and stem cell-based therapeutic procedures. Section 5 provides a discussion of the implications of the results from this study. Conclusions are postulated in Section 6.

2. Literature and Conceptual Framework

2.1. Evolution of medical knowledge

The innovation literature has converged on the conceptualization of progress of medical knowledge as an evolutionary process (Nelson and Winter, 1982), in which trial-and-error dominates the search for workable solutions (Barberá-Tomás and Consoli, 2012; Consoli et al., 2016; Consoli and Ramlogan, 2008; Nelson et al., 2011). These solutions, crystallized in the development of safe and effective therapies and diagnostic approaches, are said to be the result of the co-evolution between science and practice (i.e., understanding and technique) (Barberá-Tomás and Consoli, 2012; Gelijns et al., 2001; Nelson et al., 2011). Most often than not, these medical innovation efforts rely on the imperfect understanding of diseases, in which engineering and experimentation prevail (Barberá-Tomás and Consoli, 2012; Metcalfe et al., 2005; Nelson et al., 2011). The progress of medical

knowledge is difficult (Yaqub and Nightingale, 2012), owing to the complexity that arises from the high degree of uncertainty involved in medical fields, the complexity of the human body and the heterogeneity of human population, the complex interactions between practice and knowledge, and the disparity of the stakeholders involved (Gelijns et al., 2001).

Faced with these difficulties, recent studies have proposed more broad-encompassing approaches for assessing the progress of medical knowledge. Two main research streams stand out in the literature, namely co-evolutionary and systems-oriented perspectives. Whereas the former approach focuses on the different complementary domains involved in the development of novel technologies and their interactions, the latter emphasizes the components making up particular biomedical innovation systems, including the technologies, actors, institutions, and networks. Despite the high complementarity between both research streams, studies integrating both approaches into a single framework have not been reported yet.

2.2. Systemic and co-evolutionary views

New technologies do not grow in isolation; rather, their emergence and growth is nurtured by nascent structures consisting of technologies, actors, institutions, networks, also referred as Technological Innovation Systems (TIS) (Hekkert and Negro, 2009; Jacobsson, 2008; Markard and Truffer, 2008; Van Merkerk and Smits, 2008). These structures are in constant change, continuously adapting and re-adapting to internal and external cues. Emerging TIS are characterized by low technological performances, underdeveloped markets, and ill-defined patterns of use (Jacobsson, 2008; Musiolik and Markard, 2011). These emerging TIS are embedded into existing contexts, whether technological, organizational, or institutional in nature (Bergek et al., 2015; Jacobsson, 2008; Kukk et al., 2015; Wirth and Markard, 2011), that directly shape their development (Wirth and Markard, 2011). Consoli and Ramlogan (2008) has advanced the view of distributed healthcare innovation systems, whose engines of knowledge creation lie in the sequences of problems and solutions across clinical, medical, organizational or entrepreneurial domains (Consoli et al., 2016; Consoli and Ramlogan, 2008, 2011; Mina et al., 2007).

Several studies have conceptualized progress of medical knowledge from co-evolutionary perspectives. For example, the co-evolution between organizational configurations and patterns of scientific specialization, and thus social networks, observed in diseases and devices (Consoli and Ramlogan, 2011; Mina et al., 2007), the co-evolution between technique (or practice) and understanding (or knowledge) (Mina et al., 2007; Nelson, 2003), and so on. Morlacchi and Nelson (2011) and Nelson et al. (2011) have stressed the need to study the evolution of medical progress through three partly co-evolving, pathways: (a) basic scientific biomedical knowledge about *diseases and body functions*; (b) development of new *biomedical technologies* for medical diagnosis and treatment; and (c) learning-by-doing in *clinical practice and procedures*.

Petersen et al. (2016) made use of a triple-helix model to examine the interplay between the demand (disease)- and supply (drugs and chemicals)-related issues involved in the innovation and technological capabilities (analytic, diagnostic, and therapeutic techniques) of medical research. In their study, they emphasize the interactions among these three dimensions as crucial for the understanding and governance of the uncertainty of medical innovation. They highlighted the role of technological capabilities as the driving force in their studies, and its strongest linkage with demand. Despite the highly quantitative nature of their study, Petersen et al. (2016) approach medical innovation from a macro-meso perspective, overlooking the particularities and intricacies of particular fields of medicine at the micro level, as well as the use of other types of data besides scientific publications, such as patents and clinical trial data.

2.3. Conceptual framework

The conceptual framework of this study combines co-evolutionary and system-oriented perspectives to examine the factors influencing the evolution of emerging medical knowledge. Following Morlacchi and Nelson (2011), Nelson et al. (2011), and Petersen et al. (2016), we dissect the evolution of emerging medical knowledge into three components: disease or demand issues (in our case: AMD), biomedical technologies or technological competencies (in our case: iPS cells and related technologies), and clinical practices or supply issues (in our case: stem cell-based therapies for AMD) (Fig. 1). Each of these components is assumed to be embedded into TIS of their own, as described by Wirth and Markard (2011) (Fig. 1).

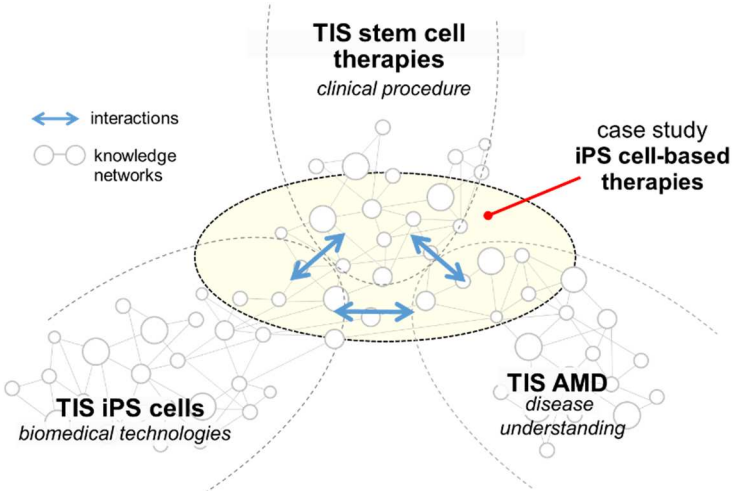

Fig. 1 Conceptual framework. Abbreviations: [TIS] technological innovation system, [AMD] age-related macular degeneration, and [iPS] induced pluripotent stem cell

From a co-evolutionary lens, we assume that an understanding of the dynamics of technologies can be gained from an exploration of the changes in their supporting knowledge structures (Ávila-Robinson, 2013; Ávila-Robinson and Miyazaki, 2013). Literature has widely acknowledged the close interrelationships between knowledge and technology (Consoli and Ramlogan, 2011; Mina et al., 2007). Knowledge does not only embody and make any technology possible (Arthur, 2009), but also its generation, testing and modification is crucial for the evolution of technologies (Loasby, 2002). Thus, modeling of these knowledge structures, observation of their patterns and dynamics of change, and exploration of their points of interaction are valuable for understanding the development and growth of new therapeutic approaches, such as iPS cell-based therapies (Fig. 1). We do so by including scientific, technological, and clinical data across disease, biomedical technology, and clinical practice domains.

3. Research design

3.1. Case study: Induced pluripotent stem (iPS) cell-based therapies for age-related macular degeneration (AMD) disease

The field of stem cells has experienced a revival with the discovery of iPS cells in 2006 at Kyoto University (Barfoot, 2013; Watatani et al., 2013). iPS cells refer to cells from mature tissues forced to return to a pluripotent state—the ability to transform into almost any cell type—by the introduction of a series of transcription factors, or proteins, in a process referred as "reprogramming" or generation (Fig. 2). This method largely circumvents the ethical and political concerns surrounding other stem cell types, such as embryonic stem cells. In a subsequent step, iPS cells can be "differentiated," i.e. converted, into almost any cell type, be it brain, heart, liver, eye, or lung cells, or any other cell (Fig. 2). Four potential application domains have been (Inoue et al, 2014): (i) research tools for drug discovery tools and toxicity testing; (ii) tools for the modeling of diseases by generating pluripotent stem cells from patients afflicted with diseases; (iii) platforms for personalized/precise medicine for customized therapeutic regimes; and (iv) cell transplantation or cell therapies (Fig. 2).

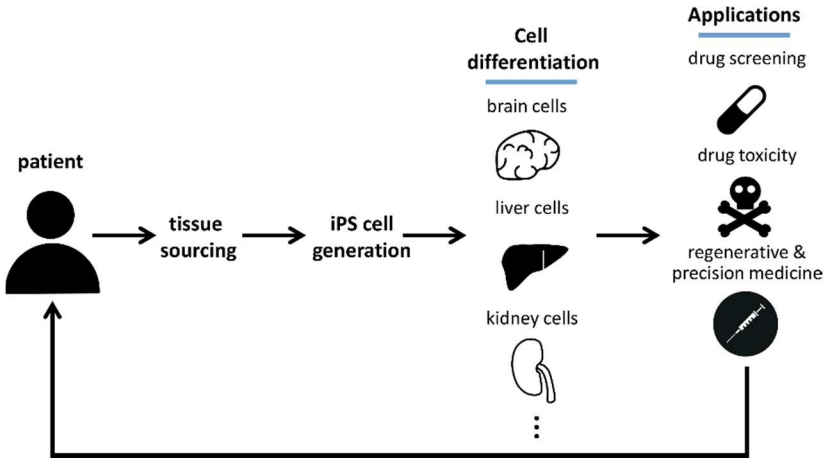

Fig. 2. General value chain of iPS cells

First identified by Otto Haab in 1885, AMD is a chronic progressive disease common in elderly people that results in the degeneration of photoreceptors and the underlying tissues, mainly the retinal pigment epithelium (RPE), in the central region of the retina, referred as macula. Compared to other eye degenerative diseases, AMD results in the loss of central vision which may not necessarily lead to the loss of vision but significantly impairs the ability of AMD patients to carry out daily-life activities such as reading and face recognition (NEI, 2017). AMD is the third most common cause of blindness after cataracts and uncorrected refractive error, but the first in the elderly of the Western world (Bourne et al., 2013). As a result of the aging of the population, particularly in industrialized countries, the incidence and prevalence of AMD is projected to grow exponentially (Wong et al., 2014). AMD is a complex disease caused by multiple genes, or polygenic, whose progression occurs in two main stages—dry- and wet-AMD—which are characterized by different clinical manifestations and burdens, as shown in Table 1.

Table 1 General characteristics of dry and wet age-related macular degeneration. Abbreviations: [RPE] retinal pigment epithelium; [BrM] Bruch's membrane.

	Dry AMD	Wet AMD
Alternative names	Non-neovascular, non-exudative	Neovascular, exudative
Clinical manifestations	Accumulation of deposits called drusen RPE and BrM, pigmentation irregularities in RPE, and functional cell atrophy in the macula	Detachment of the RPE, or choroidal neovascularization (blood vessels under the macula leading to bleeding), or both
Disease stage	Early to intermediate	Intermediate to late
General prevalence	~80% of cases	~10-20% cases, but 90% of those with vision loss

At present, there are no treatments for dry AMD; for wet AMD, there has been some success, but the existing therapeutic approaches are still palliative in nature. Thus, there is a clear unmet clinical need driving technical change in this medical field (Ramsden et al., 2016). Next, we describe the data and research methodology used to examine the use of iPS cells for the treatment of AMD disease.

3.2. Data and research methodology

To investigate the evolution of iPS cell-based therapies for AMD disease, we examined the knowledge structures underlying three constitutive components, namely disease, biomedical technologies, and clinical procedures, through the research methods described in this section.

3.2.1. Biomedical technologies: Induced pluripotent stem (iPS) cells

We analyzed the scientific and technological dynamics of knowledge related to iPS cells through the construction of term maps based on publication and patent family data. Term maps, also referred as research

landscapes, are used to dissect the cognitive structures underlying science and technology by interconnecting relevant keywords from texts (Callon et al., 1983; Van Eck and Waltman, 2010; Wallace and Ràfols, 2018). We collected iPS cell-relevant scientific publications from the Elsevier's Scopus database, focusing on publications, conference proceedings, and book chapters (protocols) published between the years 2006 and 2015. We extracted indexer keywords, author keywords, and title noun phrases from the iPS cell-relevant documents. For patent data, we harvested patent families related to iPS cell research from the Thomson Reuters' Derwent Innovations Index (DII) database. To ensure greater coverage of iPS-relevant patents, we conducted a complementary full-text patent search in the publicly available FPO database (http://www.freepatentsonline.com/). Additional patents obtained from this database were added to the pool of DII patents by identifying their patent families. We extracted cleaned terms from the titles and abstracts of these patents of iPS cell-relevant patent families. The relevant terms collected from publications and patent families form the basis for the construction of term maps. Three periods were defined for both documents: up to 2009, 2010-2012, and 2013-2015. We visualized the term maps with the use of the Pajek software (De Nooy et al., 2011). With the help of the software VOSviewer (Van Eck and Waltman, 2010), clusters were extracted from these networks and labeled according to their containing publications and patents.

To assess the clinical trajectories of iPS cell research landscapes, we extracted terms describing specific diseases from these networks. For this, we built a thesaurus with several synonyms and variations of diseases based on MEDIC disease vocabulary (Davis et al., 2012) in the Comparative Toxicogenomics Database (CTD) database (http://ctdbase.org/help/diseaseDetailHelp.jsp). We used the CTD database because it combines the subset of descriptors from the "Diseases" branch of PubMed's Medical Subject Headings—frequently used in innovation studies (Leydesdorff et al., 2012; Petersen et al., 2016)—and the database Online Mendelian Inheritance in Man® (OMIM) (Davis et al., 2012). We used the thesaurus MEDIC to identify disease-specific terms and to classify them into different phenotypical categories (e.g. cardiovascular, gastrointestinal, and musculoskeletal). The frequency with which diseases appear in publications or patents was used as an indicator of their clinical relevance.

3.2.2. Disease: Age-related macular degeneration (AMD)

To explore the dynamics of the knowledge structures supporting research on AMD disease, we used publication, patent and clinical trial data. We harvested AMD-relevant publications—excluding reviews, and letters— and patent families published up the year 2015 from the WoS and DII databases, respectively. Data collection relied on search queries containing alternative terms of AMD disease, resulting in 10,769 journal publications and 6,605 patent families, from which we extracted their cited references. We analyzed the scientific and technological knowledge dynamics of the AMD field with weighted citation networks, as dictated by the "main path analysis" approach described in De Nooy et al. (2011) and Batagelj et al. (2014), and empirically used by Mina et al. (2007), Epicoco (2013), Huenteler et al. (2016), and Yuan and Miyazaki (2017). The general methods used are as follows.

First, we constructed citation networks from AMD-relevant publications and patents. Following De Nooy et al. (2011), these citations networks were made acyclic (i.e., making all nodes pointing to the same direction in time) by coalescing strong network components and removing node loops. In addition, the edges of these networks were weighted with the traversal weight function "search path function" (SPC) and normalized with the "Normalize-Flow" functions of the Pajek software. These procedures normalize edges by the extent to which they are involved in the total of paths flowing from the sink to the source nodes of a citation network. Thus, the higher the edge values, their greater their participation in the processes of knowledge accumulation in a research field (De Nooy et al., 2011). The main network components were subsequently visualized with the Pajek software. We classified the publications and patents of these networks into the main problem areas they tackle, based on the contents of their texts, including: "Quality of life," "Pathogenesis," "Diagnosis," and "Therapeutic approaches." Subsequently, we evaluated the distribution of problems across the citation network and the level of interconnections between problems.

Clinical trial data on AMD disease were collected from the clinicaltrials.gov database for clinical trials registered in the U.S. National Institutes of Health (NIH) and the International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/Default.aspx) of the WHO, which includes additional 16 countries. We used the broad search query "macular degeneration" to maximize clinical data coverage. We considered all types of clinical trials – ongoing, completed, terminated, and withdrawn – registered until 2015. From these

clinical trials, we extracted information on their type of intervention and their phases of clinical study for further evaluation.

3.2.3. Therapeutic procedures: Stem cell-based therapies for AMD disease

This section describes the patterns of dynamics occurring in the knowledge structure delimiting the stem cell-based therapeutic procedures for AMD. To study these dynamics, we first identified publications and patent families up to September 2016–from the WoS and DII databases, respectively–using terms relevant to stem cell transplantation approaches for AMD. We assessed these documents based on their relevance to the transplantation or administration of stem cells, at any stage of technological development, for the treatment of macular degenerative diseases. In particular, we evaluated the "Materials and Methods" or "Experimental Procedures" sections of publications and patent claims to assess the general properties of their therapeutic approaches. Subsequently, we built a single citation matrix integrating both citing and cited documents from publications and patent families dealing with stem cell therapies for AMD disease.

Following similar procedures described in Section 2.2.2, we applied SPC weights and "normalize-flow" normalization to the integrated citation network using Pajek software. Based on Horlings and Gurney (2013)'s study on the search paths of researchers, we arranged the integrated citation network along two axes describing the characteristics of the stem cell-based therapeutic procedures proposed for treating AMD disease. This classification includes aspects, such as source of transplanted cells, cell delivery method, type of transplantation, mode of cell administration, and type of experimental model. To visualize the integrated citation network we used the layout arrangement approach proposed by Horlings and Gurney (2013), which makes use of Gephi software's geolayout algorithm. The following latitude (x-axis) and longitude (y-axis) values were used: latitude as [(problem area) / (total number of problem areas) × 180] – 90; and longitude as [(year of publications) – (year of first publication in dataset) / (range of years) × 360] – 180. Recently, similar analyses have been conducted by Huenteler et al. (2016) and Stephan et al. (2017).

We then conducted a series of interviews with key stem cell researchers and principal investigators for AMD cell therapies to explore further the results of this study. Our interviews included researchers in Japan (Kyoto University's Center for iPS Cell Research and Application) and the United States (University of California Santa Barbara's Center for Stem Cell Biology and Engineering and Center for the Study of Macular Degeneration, and University of Southern California's Roski Eye Institute). We used open-ended questionnaire that resulted in semi-structure discussions lasting each approximately 40 minutes to an hour.

4. Results

This section describes the results of this study. High resolution images of the figures presented in this section can be found at https://sites.google.com/site/ipscelltherapies/.

4.1. Knowledge structures underlying research on induced pluripotent stem (iPS) cells

To describe the dynamics of the scientific and technological knowledge structures underlying research on iPS cells, we built term maps by extracting keywords from iPS cell-relevant publications and patent families published up to 2015 (Fig. 3).

[Insert Fig. 3 here]

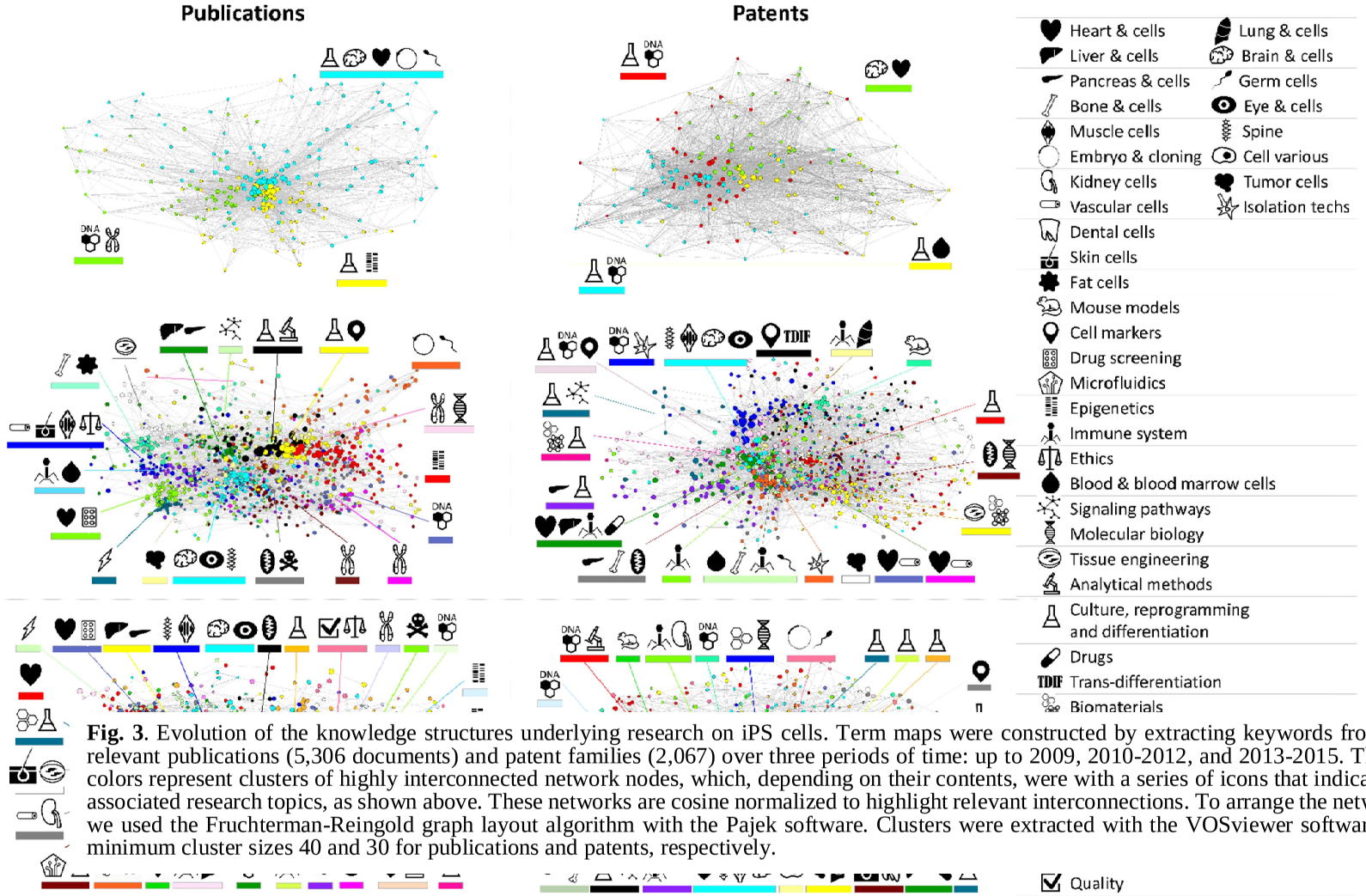

Fig. 3. Evolution of the knowledge structures underlying research on iPS cells. Term maps were constructed by extracting keywords from iPS cell-relevant publications (5,306 documents) and patent families (2,067) over three periods of time: up to 2009, 2010-2012, and 2013-2015. The different colors represent clusters of highly interconnected network nodes, which, depending on their contents, were with a series of icons that indicate the main associated research topics, as shown above. These networks are cosine normalized to highlight relevant interconnections. To arrange the network nodes, we used the Fruchterman-Reingold graph layout algorithm with the Pajek software. Clusters were extracted with the VOSviewer software using the minimum cluster sizes 40 and 30 for publications and patents, respectively.

Three periods of time were defined: up to 2009, 2010-2012, and 2013-2015. The colors of the nodes of the network nodes in Fig. 3 represent clusters of highly cognitively interrelated terms. For visualization purposes, these clusters are tagged with a series of icons that indicate the main associated research topics.

At first sight, Fig. 3 demonstrates the explosive growth experienced by iPS cells beginning in 2009. This growth is not only reflected in the total of terms making up these networks but also in the increasing number and diversity of their clusters over time. After evaluating these clusters, we observed that the networks in Fig. 3 can be divided into two broad cognitive categories: (i) clinical research-dominated clusters containing terms related to organs and tissues (e.g. heart, liver, bone and muscle) and (ii) basic research-dominated clusters that focus on gene delivery approaches necessary for the generation and differentiation of iPS cells, gene-editing approaches, and cell culturing methods. The division observed in the maps of Fig. 3 resembles the epistemological segmentation of research organization in the field of iPS cells. An analysis of emerging topics reveals that enabling technologies such as genome editing through CRISPR-Cas9 technologies, purification or isolation through messenger ribonucleic acid, and next generation sequencing technologies show the greatest recent rates of growth. In particular, genome-editing CRISPR-Cas9 technologies have significantly influenced the field of iPS cells by allowing the development of cell-based assays through the introduction of disease-causing mutations into healthy cells, and the development of gene therapies through the correction of disease-causing mutations in diseased cells and their transplantation into patients.

Biomedical knowledge is unique in that it is created with clinical aims in mind, i.e. the cure, treatment, and/or prevention of diseases, illnesses, or disorders that involve safe, effective, and feasible diagnostic or therapeutic technologies. Hence, better insights into the progress of biomedical technologies such as iPS cells can be gained by ascertaining their clinical potential, as inferred from the targeted diseases. For the remaining of this section, we analyze disease-specific terms extracted from the term maps of Fig. 3.

In Fig. 4, we classified the clusters obtained in Fig. 3, according to their contents, into more basic- or clinical-oriented research, as seen in the blue- and yellow-colored nodes, respectively. Disease-specific terms are highlighted in Fig. 4 with black dots. The results of this figure show that the number of disease-specific terms significantly increased in the last two periods of time for publication- and patent-based research landscapes. This resonates with the clinical-oriented trajectories along which research on the field of iPS cells has been channeled since its inception by Yamanaka and colleagues (Yamanaka, 2009, 2013). Fig. 4 also shows differences in the distribution of diseases in the publication- and patent-derived networks. Disease-specific terms from patents tend to concentrate in the middle of the networks, whereas those from publications spread more evenly throughout the networks. This may be attributable to the intrinsic differences in the drafting of publications and patents; for instance, the claims of patents tend to be drafted as broad as conceivable to embrace as many diseases as possible.

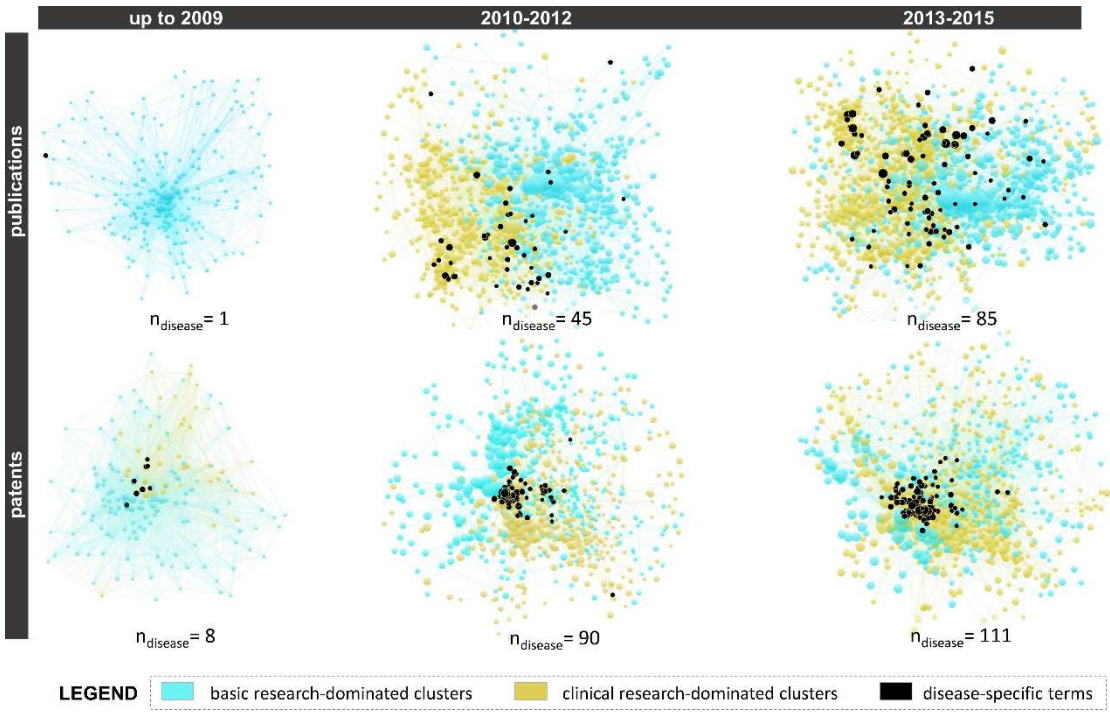

Fig. 4. Evolution of disease-related terms over time in publications (top networks) and patents (bottom networks). These networks depict the networks of Fig. 3 for iPS cell-relevant publications and patents across three periods of time: up to 2009, 2010-2012, and 2013-2015. Colors represent basic research-dominated clusters (blue), clinical research-dominated clusters (yellow), and disease-specific terms (black). Networks were visualized with the VOSviewer software. $n_{disease}$ indicates the number of disease-specific terms.

Fig. 5 illustrates the trajectories of growth experienced by iPS cell research across disease categories and specific diseases, as inferred from normalized intensity research indices for publications and patents. Fig. 5a displays the highly biased growth of iPS cell research on nervous system and cardiovascular diseases, followed by metabolic diseases to a lesser degree. No significant differences in indices were observed between publications and patents, with the exceptions of those associated with endocrine, musculoskeletal, and immune diseases. For both publications and patents, respiratory, skin, and urogenital diseases showed the lowest intensities.

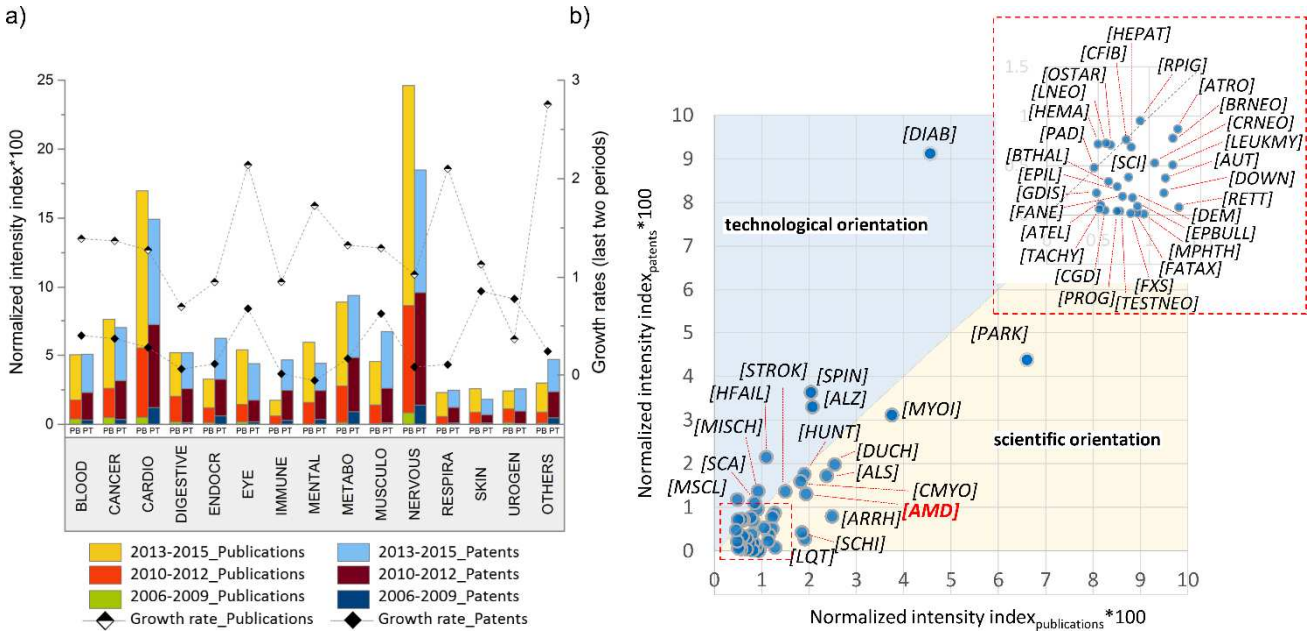

Fig. 5. Clinical potential of induced pluripotent stem cell publications and patents. Fig. 5a displays the trajectories of growth experienced by iPS cell research across disease categories, in terms of normalized intensity indexes (bar charts) and growth rates (line charts) for 1,585 publications and 838 patents with disease terms. Fig. 5b locates top-50 diseases with the highest normalized intensity indices along scientific (x-axis) and technological (y-axis) domains. For both figures, we used a two-step normalization: fractionalized term instances and normalization by total of publications/patents. According to their position, diseases fall into areas of higher scientific or technological orientation. Abbreviations used are as follows:

- Disease categories: [BLOOD] hematological diseases; [CANCER] cancer diseases; [CARDIO] cardiovascular diseases; [DIGESTIVE] gastrointestinal diseases; [ENDOCR] endocrine disease; [EYE] ophthalmological diseases; [IMMUNE] immune system diseases; [MENTAL] mental diseases; [METABO] metabolic system diseases; [MUSCULO] musculoskeletal diseases; [NERVOUS] nervous system diseases; [RESPIRA] respiratory system diseases; [SKIN] skin diseases; [UROGEN] urogenital diseases; [OTHERS] other diseases.
- Specific diseases: [ALS] amyotrophic lateral sclerosis; [ALZ] Alzheimer's disease; [ARRH] cardiac arrhythmias; [ATEL] ataxia telangiectasia; [ATRO] spinal muscular atrophy; [AUT] autistic disorder; [BRNEO] breast neoplasms; [BTHAL] beta-thalassemia; [CFIB] cystic fibrosis; [CGD] chronic granulomatous disease; [CMYO] cardiomyopathies; [CRNEO] colorectal neoplasms; [DEM] dementia; [DIAB] diabetes mellitus; [DOWN] Down syndrome; [DUCH] Duchenne muscular dystrophy; [EPBULL] epidermolysis bullosa; [EPIL] epilepsy; [FANE] Fanconi anemia; [FATAX] Friedreich ataxia; [FXS] fragile X syndrome; [GDIS] Gaucher disease; [HEMA] hemophilia A; [HEPAT] hepatitis; [HFAIL] heart failure; [HUNT] Huntington disease; [LEUKMY] myeloid leukemia; [LNEO] liver neoplasms; [LQT] long QT syndrome; [AMD] macular degeneration; [MISCH] myocardial ischemia; [MPHTH] microphthalmos; [MSCL] multiple sclerosis; [MYOI] myocardial infarction; [OSTAR] osteoarthritis; [PAD] peripheral arterial disease; [PARK] Parkinson's disease; [PROG] progeria; [RETT] Rett syndrome; [RPIG] retinitis pigmentosa; [SCA] sickle cell anemia; [SCHI] schizophrenia; [SCI] severe combined Immunodeficiency; [SPIN] spinal cord injuries; [STROK] stroke; [TACHY] tachycardia; [TESTNEO] testicular neoplasms.

Fig. 5b indicates that the unevenness of the trajectories of growth in iPS cell research is more marked at the level of specific diseases. This figure locates the top-50 diseases based on their normalized intensity indices for publications and patents, on the x and y axes respectively. Two outlying diseases can be observed in this figure: diabetes *[DIAB]* and Parkinson's disease *[PARK]*. These diseases are followed in intensity by Alzheimer's disease *[ALZ]*, spinal cord injuries *[SPIN]*, and myocardial infarction *[MYOI]*. At lower intensity levels, we find Huntington's disease *[HUNT]*, Duchene muscular dystrophy *[DUCH]*, amyotrophic lateral sclerosis *[ALS]*, cardiomyopathies *[CMYO]*, stroke *[STROK]*, heart failure *[HFAIL]*, and age-related macular degeneration *[AMD]*. Out of those diseases for which iPS cells have been applied therapeutically, AMD has been the only disease whose therapeutic approach has been translated into a clinical, albeit at still exploratory, pre-clinical stages.

Depending on the location of diseases, their trajectories of growth are more scientifically or technologically driven, as shown by the different colors in Fig 5b. Two extremes, although with different intensity levels, are the highly technologically oriented diabetes and the highly scientifically oriented long QT syndrome *[LQT]*, a heart rhythm condition, and schizophrenia *[SCI]*. It should be noted that the diseases extracted from this section do not necessarily refer to cell therapies, as iPS cells can also be used in other application domains such as "disease modeling" and "drug screening/toxicology," as described in Section 3.1. In fact, the use of iPS cells as cell therapies is limited to those diseases caused by the loss of function of a single type of cell (Ravven, 2017).

4.2. Knowledge structure underlying research on age-related macular degeneration (AMD) disease

To investigate the dynamics of the scientific and technological knowledge structures underlying research on AMD disease, we obtained weighted citation networks from AMD-relevant publications and patents. For this, we used the "main path analysis" approach, proposed by Consoli and Ramlogan (2008), De Nooy et al. (2011), and Mina et al. (2007), which pinpoints those nodes and connections linking most of the documents. We classified the nodes of these networks based on the taxonomy of general problem areas shown in Table 2.

Table 2 General problem areas for the field of AMD research.

Problem area	Description
Quality of life	This refers to those aspects related to the well-being of AMD patients, including their physical and psychological health, their ability to carry out general and vision-related daily-life activities (e.g. driving, reading, and face recognition), and economic aspects related to AMD.
Pathogenesis	This involves the study of the factors that initiate and maintain AMD, its etiology, the molecular and cellular mechanisms and pathways of AMD, and risk factors associated with the susceptibility to AMD, including environmental (smoking, diet, light exposure, disease associations, and ethnic/demographic characteristics) and genetic factors. It also includes epidemiological studies to determine the prevalence and incidence of AMD, as well as the associations between AMD and other diseases.
Diagnosis	This encompasses those studies aimed at assessing the clinical manifestations and phenotypic characteristics of the disease, i.e., the observable features of organisms with AMD. This includes the use of biomarkers or clinical markers, histopathological approaches to understand the influence of AMD on retinal cells and tissues, experimental animal/cell model systems, studies to characterize the AMD phenotype through imaging and instrumentation methods, as well as risk assessments and evaluation of disease progression.

Therapeutic approaches	This refers to approaches to treat and manage AMD. It also includes proof-of-concept studies of therapeutic methods, follow-up studies from clinical trials, pharmacogenetic studies of genes associated with responses to particular therapies, association studies between therapies and histopathology, and basic research efforts highly oriented toward therapies.

The nodes of the networks in Fig. 6 represent either publications (Fig. 6a) or patent families (Fig. 6b). The colors of the network nodes represent a finer classification of the general problem taxonomy of Table 2.

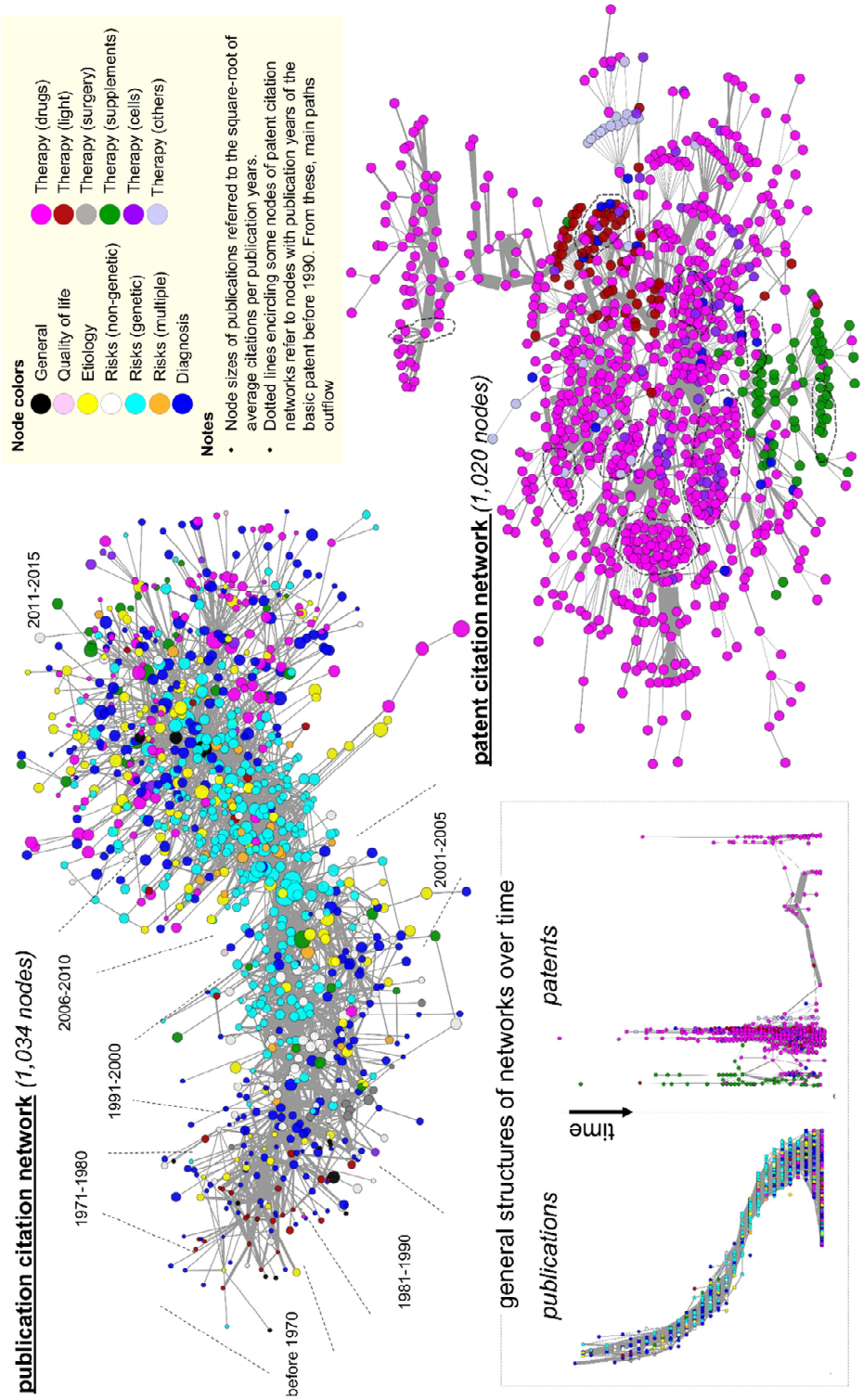

Fig 6. AMD scientific and technological knowledge structures. The top and bottom-right networks depict the weighted scientific and technological citation networks, respectively, obtained from the collected data (1,034 publications and 1,020 patent families). Node sizes of scientific articles refer to the square root of average citations per years after publication. The dotted lines encircling some of the nodes of the patent citation network represent nodes with publication years of basic patent before 1990. From these, main paths outflow. Colors

The results of Fig. 6 top suggest that the evolution of the scientific knowledge structure on AMD disease converges from the early 2000s into the study of cellular and molecular mechanisms underlying AMD disease,

i.e., its etiology and the genetic and environmental factors associated with susceptibility of disease (yellow, white, cyan and orange nodes). These pathogenesis-related activities make up the focus of scientific activity accounting for more than half of the network nodes, as shown in Table 3a. The significant efforts addressing a basic understanding of AMD pinpoint the complex and multi-factorial nature of this disease, even after hundreds of years of its discovery.

Table 3 Cross-citations between general problem areas in terms of percentage shares (top part of cells) and average publication years (bottom part of cells) for AMD's a) scientific knowledge structure and b) technological knowledge structure.

a)

citing \ cited	General	Quality of Life	Pathogenesis	Diagnosis	Therapies
General	- -	- -	1% 2012.7	- -	- -
Quality of Life	- -	- -	- -	- -	- -
Pathogenesis	1% 2009.7	- -	52% 2005.4	7% 2001.9	2% 2008.4
Diagnosis	1% 1999.7	- -	9% 2001.9	12% 1996.9	2% 1995.5
Therapies	1% 2008.1	- -	4% 2007.9	2% 2000.3	6% 2003.6
Total nodes	1.3% 1979.2	0.3% 2011.0	50.4% 2004.4	27.4% 1997.4	20.6% 2006.6

b)

citing \ cited	General	Quality of Life	Pathogenesis	Diagnosis	Therapies
General	- -	- -	- -	- -	- -
Quality of Life	- -	- -	- -	- -	- -
Pathogenesis	- -	- -	- -	- -	- -
Diagnosis	- -	- -	- -	0.1% 2008	1% 2008.9
Therapies	- -	- -	- -	1% 2002.8	98% 2004
Total nodes	- -	- -	- -	2% 2003.5	98% 2002.4

In Fig. 6 top, it can be seen how knowledge in the field of AMD disease appears to be accumulated in distinct areas over time, moving from initial knowledge accumulation on the pathogenesis, etiology, and risks of AMD to the development and use of different imaging techniques and the development of alternative therapeutic approaches. However, this progression is far from linear, as observed in the percentage of cross-citations between the general problem areas shown in Table 3a. Cross-citations are mostly limited within the same problem areas, accounting for about 70% of the total cross-citations. For cross-citations between different problem areas, only those between "Diagnosis" and "Pathogenesis" are particularly prevalent, yet their average publication years are low relative to other problem area interactions. Here, detection and monitoring technologies, such as retinal imaging technologies and technologies for genetic studies (e.g. genome-wide association studies or next generation sequencing technologies) play a major role in advancing basic understanding of disease, as discussed below.

Pathogenesis-therapies cross-citations show high levels of interaction. Two aspects should be highlighted. First, traditional approaches for elucidating the causes and progression of AMD disease, such as epidemiological data, clinical observations, histopathological data, and biochemical studies can provide key insights into the discovery of potential therapeutic avenues. Second, as the understanding of the common genetic variants of AMD disease accumulates, particularly through the discovery of appropriate biomarkers, greater assessments of risk to patients ("patient stratification") and the development of "precise" or "personalized" therapies may come about (Amir-Aslani and Mangematin, 2010; Gittelman, 2016; Propp and Moors, 2009).

Fig. 6 top also indicates the evolution of the different therapeutic paradigms established in the field of AMD from the 1970s. Beginning with the "rough" surgical procedures of the late 1970s in which retinal tissue was mechanically removed (gray nodes), AMD therapies moved to laser approaches with photocoagulation in the 1980s (brown nodes). Here, an Argon laser was used to cauterize the invading blood vessels common in late-stage, or wet, AMD. In the early 2000s, photodynamic therapies followed in which a laser was used to destroy specifically blood vessels that had previously absorbed a photosensitizer material injected into the eye (brown nodes). The in-take of dietary supplements such as vitamins and minerals has been an approach in use since the early 1990s (green nodes). Drug-based approaches have overtaken the therapeutic landscape of AMD in recent years (dark pink nodes). Some examples with their years of approval from the U.S. Food and Drug

Administration are the following: pegaptanib sodium or Macugen® (2004), ranibizumab or Lucentis® (2006), aflibercept or Eylea® (2011), and bevacizumab or Avastin®. Interestingly, Avastin® is a repurposed drug that was originally developed by Genentech for advanced colorectal cancer, which compared to Lucentis®, the gold-standard therapy, is almost 40 times cheaper. This drug repurposing strategy was possible through the understanding of the pathogenesis mechanism of wet-AMD, namely the crucial role of blood vessel growth.

At the fringes of this network, we find nodes related to cell-based therapies (purple nodes). The scientific knowledge structure of Fig. 6 top also shows that growth of therapies has proceeded in concert with the intense research on genetic factors, i.e. mutations and polymorphisms, associated with AMD disease (cyan nodes). As shown in Fig. 6 top, imaging techniques, such as optical coherence tomography, laser photocoagulation, and fundus auto-fluorescence imaging are central in the knowledge structure of AMD disease. These activities appear to be influential both in the early and late phases of scientific development.

In contrast, the technological knowledge structure of Fig. 6 bottom-right displays a different picture of the dynamics of AMD disease. Unsurprisingly, as we focus on citing-cited relationships between patents, the technological knowledge structure is highly dominated by therapeutic approaches (Table 3b). Drug-based therapeutic approaches, which account for four-fifths of the nodes, are particularly prominent (dark pink nodes of Fig. 6 bottom-right). These approaches address problems related to the synthesis of potentially therapeutic chemical compounds, production of pharmaceutical compositions, and development of devices for the controlled delivery of drugs into the eye. The rest of the therapeutic approaches—dietary supplements, light and radiation-based approaches, and cell-based therapies—show single-digit shares. Compared to the scientific knowledge structure whose structure is mostly linear, the technological knowledge structure is characterized by several dispersed trajectories (inset in Fig. 6 bottom-left) involving different therapeutic approaches. This may be attributable to the sparser nature of the patent citation networks.

In an additional study, the clear dominance of the drug-based "regime" in the therapeutic landscape has been confirmed with the analysis of clinical trial data, as shown in Supplementary Information 1, in which we observed over 100 and 30 drugs being tested for wet- and dry-AMD disease, respectively. In total, they account for more than 80% of clinical trials. Interestingly, the recombination of new and established therapeutic technologies was a common phenomenon. In contrast, cell-based therapies—including stem cells, gene therapy, and neuroprotective therapies (i.e., in which trophic factors are used to stimulate tissue)—make up for 3% of clinical trials, and still occupy the initial stages in the clinical trial pipeline.

4.3. Knowledge structure underlying stem cell-based therapeutic approaches for AMD

In order to explore the dynamics of the knowledge structure underlying stem cell-based therapeutic procedures for AMD disease, we integrated publications and patents relevant to stem cell therapies into a single SPC-weighted citation network. In addition, we included clinical trials registered to date. Relevant publication, patent, and clinical trial data were categorized according to classification scheme of Table 4.

Table 4 Classification of the characteristics of stem cell-based therapeutic procedures.

Characteristics	Description	Levels
Basic understanding	This includes studies focusing on the basic understanding issues on the eye and its tissues	-
Stem cell-based therapies		-
Source of transplanted cells	This refers to the type of cell used in the transplantation approach, including neural stem cells, non-neural stem cells, adult cells (e.g., retinal tissue such as retinal pigment epithelium (RPE) or photoreceptors), retinal precursor cells, and pluripotent stem cells, such as induced pluripotent stem (iPS) cells and embryonic stem (ES) cells.	▪ iPS cells ▪ ES cells ▪ Other cells ▪ Photoreceptors and photoreceptor precursor cells ▪ RPE cells ▪ Non-neural stem cells ▪ Retinal progenitor cells ▪ Neural stem cells
Cell delivery method	This includes the type of method used to deliver the transplanted cells. The approaches assessed were the use of cell monolayers without any support, and the use of monolayers with scaffolds.	▪ Monolayer ▪ Monolayer and scaffold ▪ Suspension ▪ Others/multiple approaches
Type of transplantation	This refers to the type of cells used for transplantation. Autologous refers to cells from the same individual that receives the cells, and	▪ Autologous [AUTO] ▪ Allogeneic [ALLO]

	allogenic refers to those for which donor and receipt are different. In allogenic transplantation, we included xenogeneic approaches in which cells from different species are used.	▪ Other/various approaches [OTHER]
Mode of cell administration	This refers to the surgical procedure used to deliver cells into the eye, either sub-retinal, i.e. underneath the retina, or intravitreal, i.e. directly into the eye. Additional methods were included in the "Others" category.	▪ Sub-retinal delivery [SR] ▪ Intravitreal delivery [IV] ▪ Other/various approaches [OT]
Type of experimentation model	This describes whether the model of transplantation used is of animal or human origin.	▪ Animal ▪ Human
Other therapeutic approaches and diseases	This includes other types of therapies besides stem cell-based therapeutic methods and diseases	-

Fig. 7 shows the schematic that results from accommodating the nodes of the techno-scientific citation network into a matrix delimiting the main characteristics of stem cell therapies, illustrated in Table 4. The shapes of the nodes in Fig. 7 represent document types—publications (circles), patents (triangles), and clinical trials (squares)—related to stem cell-based therapies for AMD. The colors of these nodes indicate the years, as described in Fig. 7; red-colored nodes indicate the latest publication period. The lines connect publications and patents according to their normalized citation relationships, whose colors represent the types of stem cell being used in the particular therapeutic procedure addressed in the documents, corresponding to the cited node. We replicated those nodes when a document addressed multiple stem cell types. Clinical trial nodes are superimposed into the matrix without being connected to publication or patent nodes.

The knowledge structure of Fig. 7 indicates the co-existence of multiple solutions of stem cell-based therapeutic procedures for AMD disease, including sources of transplanted cells, delivery methods, types of transplantation, modes of cell administration delivery approaches, surgical techniques, and immuno-suppression strategies. According to the number and thickness of the network lines, the flows of knowledge are dominant across embryonic stem (ES) cell-, retinal pigment epithelium (RPE) cell-, and retinal progenitor cell-based therapeutic procedures. These were followed by those procedures relying on induced pluripotent stem (iPS) cells, neural stem cells, photoreceptor precursor cells, and non-neural stem cells (e.g., umbilical cord stem cells, bone marrow stem cells, and mesenchymal stem cells). However, when publication years of the nodes—publications or patent—are considered, Fig. 6 shows that ES and iPS cells and non-neural stem cells are at the forefront of the current research as they show the largest number of red-colored nodes, followed by photoreceptor precursor cells, neural stem cells, and retinal progenitor cells. Despite their many nodes, RPE cells are associated with the oldest publication years. This is not surprising as this type of cell was used in the earliest attempts to test transplantation of cells for AMD treatment.

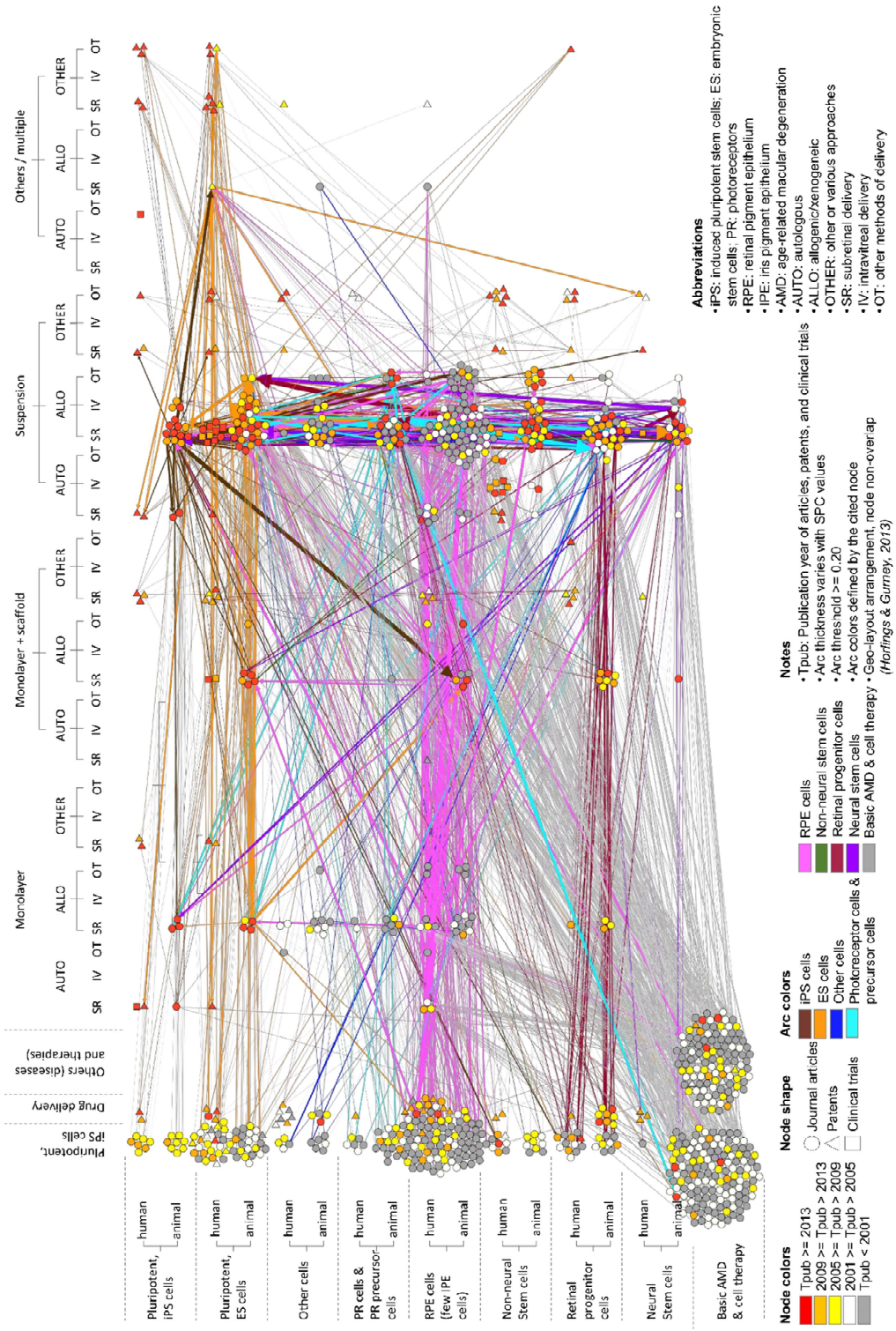

Fig. 7. Dynamics of the knowledge structure underlying stem cell-based therapies for AMD disease. 233 publications (circle nodes) and 93 patents (triangle nodes) relevant to cell therapeutic approaches for AMD , and their cited, patent and non-patent references, were integrated into a single weighted citation network following the "main path analysis" approach described by De Nooy et al. (2011). The nodes of these networks, including clinical trials (square nodes) are accommodated into a matrix delimited by the main characteristics of cell therapeutic approaches described in Table 4. The colors of the nodes vary according to the year of publication of the nodes. Moreover, arc thickness change depending on their normalized SPC values. The colors of the arcs correspond to the type of cell involved in the cited node. To arrange the different nodes, we used the geo-layout approach in Gephi software, as described by Horlings and Gurney (2013).

Viewed vertically, the dominance of subretinally delivered suspensions of allogeneic stem cells—stem cells from which donor and receipt are different—is apparent; this is followed by the use of monolayers or sheets, and, to a less degree, sheets combined with bio-engineered scaffolds. However, all three approaches are being pursued actively by stem cell researchers, as each of them are characterized by their own advantages. For instance, the delivery of cells through suspensions is lower in complexity as they do not require the more complicated surgical procedures and equipment or tissue engineering-related knowledge of transplantation approaches using sheets and scaffolds. However, suspensions of stem cells are believed to suffer from lower rates of engraftment. In addition to the direct transplantation of cells, additional approaches such as the provision of trophic factors to enhance cell regeneration are also emerging.

As shown in Fig. 7, the citation connections between alternative stem cell-based therapies are relatively weak, except for solution-based delivered approaches. When organizations conducting clinical trials for AMD are considered, Fig. 7 shows that most appear to support a specific solution for stem cell transplantation to treat AMD, without diversifying into other stem cell domains or delivery methods.

5. Discussions and implications

In this paper, we investigated the evolution of emerging stem cell therapies as they transition into medical practices. Our study used the case of induced pluripotent stem (iPS) cell-based therapies for the treatment of age-related macular degeneration (AMD) disease. We used a research approach that combines co-evolutionary and systemic approaches. We assumed that deeper insights into the evolution of emerging therapeutic technologies could be gained by examining the knowledge structures that underlie three constitutive components, including disease, biomedical technologies, and clinical practices, through the use of science, technology, and clinical data. A mixed-methods approach that relies on scientific, technological and clinical-based data was used to operationalize this model. Interpreting from the results of the previous sections, we discuss the four factors influencing the evolution of emerging cell therapies. A series of policy implications drawn from these discussions are to be described below.

5.1. Influencing four domains in stem cell therapies

Based on the results of the previous section, below we discuss the four factors influencing the evolution of emerging cell therapies. These discussions were supported with the mind map of Supplementary Information 2.

Level of technological possibilities

Our results demonstrated the high levels of technological possibilities that pervade across disease, biomedical technology and clinical procedure domains of treatments for AMD. This is not surprising as the existence of multiple solutions is a prominent characteristic of the early stages of technological development (Nelson et al., 2011). Particularly, this is applicable for diseases such as AMD that are still in need for curative solutions. In addition, we observed that, stem cell researchers across the world have advanced several unique alternative transplantation techniques, strategies, and paradigms for the treatment of AMD disease. Discussions with stem cell researchers highlighted the need for such technological differentiation owing to intellectual property and technology licensing strategies of their proprietary protocols and early proofs-of-concept of their cell therapy approaches.

Contrary to common conceptions, the case of AMD demonstrates that the variety of therapeutic approaches is not mutually exclusive (Mason et al., 2011), but highly complementary in nature, contingent on the characteristics of the AMD disease. We elaborate on two main issues. Firstly, the existence of multiple therapeutic solutions appears to be enhancing the chances for recombination of therapies. This is clearly seen among the several treatments that harness the synergies of the integration of different therapeutic approaches, particularly to target patients who do not respond to mono-therapies. Another variety-generating pattern is the re-use of already existing therapeutic technologies for other indications, also referred as drug repurposing. Secondly, we found that this variety is highly related to the characteristics of AMD disease. As a complex degenerative disease, AMD disease progresses through multiple stages of severity and it is caused by multiple genetic mutations and environmental cues (Silva et al., 2015). Each of the AMD disease sub-types is characterized by specific drivers and needs, which demand the development of different therapeutic approaches (Wiley et al., 2015). Thus, for complex diseases such as AMD, we would expect to observe a “patchwork” of several co-existing therapeutic options, and even in an integrated manner with each other. Each of these therapies fills in one or more therapeutic market segments such as disease stages, severity, or genotypes, within which competitive forces may be influential. The choice of the appropriate therapeutic option may depend on the degree of understanding of the cause or mechanism of the AMD disease, or simply on economic reasons (Wiley et al., 2015).

Relationships between established and emerging technologies

As the variety of technological possibilities increases, the asymmetries between incumbent (regime) and emerging (niche) technologies become more evident. Throughout this study, we observed the dominance of the drug-based regime over the emerging cell-based therapy niche in the therapeutic landscape of AMD disease.

Regime-niche asymmetries occur not only due to their differing size and (im)maturity, but also due to the different nature driving their evolution (Geels, 2002). For instance, the drug-based therapies are dominated by the big pharma-industry, which tends to rely on the discovery of blockbuster drugs and mass manufacturing (Schachter, 2014). The drug-based regime is highly dynamic as inferred from the hundreds of different types of drugs being developed and tested in clinical trials. In contrast, the stem cell therapies mostly focus on individualized markets, are expensive to produce, have short shelf-life spans, require skilled healthcare workers, and evolve around a complex regulatory environment (Schachter, 2014). As described above, regime-niche interactions are highly complementary and synergistic through recombination, re-use, or new discovery patterns of innovation.

Directions of search

As inferred from the multiple diseases tackled in the field of iPS cells, multiple *directions of search* co-exist (see Section 4.1). Interestingly, despite its relatively low scientific and technological research intensities (see Section 4.2), AMD is the only disease that has reached a clinical stage with iPS cells, even if at an exploratory level. The reasons for this are manifold. For instance, the disease prevalence and incidence have played a role in the decision making of Japanese and American researchers, to focus on wet and dry AMD respectively, as each of these disease sub-types are more common in their respective countries. It is also not surprising that the majority of the key translational efforts on AMD disease have taken place in established life science-oriented innovation ecosystems (e.g. California, London, and the Kobe-Kyoto region in Japan) (Schachter, 2014). In addition, path-dependency has played a role as many countries with strong embryonic stem cell competencies have been able to keep up with their leadership in the field of iPS cells.

Although disease prevalence and incidence shape the directions of search, our case study demonstrated that technological and biological aspects have played a key role in the advancement of stem cell therapies for AMD. For instance, the eye is relatively an accessible organ and there are mature surgical methods and instrumentation that allow assessment and monitoring of the effectiveness of therapies for eye diseases. In addition, fewer cells are required and their differentiation protocols are advanced. Most importantly, the eye is relatively isolated from other organs and has been regarded as an "immune-privileged site," and thus, less prone to tumor formation, which is one of the main drawbacks of using stem cells in other organs (Kimbrel and Lanza, 2015; Ramsden et al., 2016; Trounson and DeWitt, 2016). Hence, the eye is an ideal—safer, less risky, and relatively less complex—organ model for experimentation with stem cells for therapies. In a sense, the eye appears to be hedging against the uncertainties and risks associated with emerging clinical practices, such as stem cell-based therapies. As such, the eye is serving as an experimentation model to assess the potentials and limits of therapeutic approaches for the human body as a whole (Dobbs, 2016; Perkel, 2014). Such "experiment-ability" is considered a crucial issue in the progress of medical knowledge (Nelson et al., 2011).

Product-process interdependencies

The development of safe and effective cell-based therapeutic approaches is circumscribed by a value chain of processes that involve a series of upstream (e.g. proof-of-concepts and pre-clinical stage activities) and downstream activities (e.g. scaling production, manufacturability, and standardization). In this context, *product-processes dependencies* of clinical practices are of relevance. In fact, in stem cell-based therapies it is well known that "the process is the product." This is highly related to the "living" nature of cell products. Such product-process dependencies have been observed in other high-technology fields in which products and processes highly interact, such as nanomaterials and other process-driven sectors (Linton and Walsh, 2008). Owing to the strong coupling between the design of products and processes, changes that occur in upstream activities can complicate downstream activities, such as translation, and commercialization activities (Dodson and Levine, 2015). For instance, modifications at downstream activities (e.g., new manufacturing processes) may result in new product specifications, which for regulatory agencies can consider as a new product that requires additional rounds of clinical trials (Prescott, 2011).

This factor also involves a wide range of organizational technologies necessary for the development of safe and effective stem cell-based therapeutic approaches. In particular, human applications demand the development of clinical-grade cell lines, which include the implementation of controlled production processes to manufacture cell products for human use, also regarded as Good Manufacturing Practices (GMP). GMP involves the scaling-up of production (e.g., facilities and equipment, personnel, supplies and reagents, manufacturing processes, laboratory controls, and packaging and distribution) and standardization (Bharti et al., 2014; Sengoku et al.,

2011). These different aspects result in the development of particular business models, including centralized and decentralized approaches, and allogeneic or autologous methods, in which patients receive cells from donors or from their own cells, respectively (Smith, 2010; Trainor et al., 2014).

As stem cells therapies are regarded as medical products, they follow the multi-phase drug pipeline process (e.g., pre-clinical to Phase I to III human clinical trials) and by obeying the approval guidelines of regulatory bodies (Trounson and DeWitt, 2016). These regulations differ across national and regional authorities (Andrews et al., 2014), which should be considered for their global deployment, including insurance reimbursement approaches, ethical issues, and standardization (Neofytou et al., 2015). Equally important is the role of lobby and patient advocacy groups (Ramsden et al., 2016). Although this study did not explicitly examine interdisciplinarity, we should clarify the importance of high degrees of knowledge interaction and collaboration among biologists, physicists, ophthalmologists, clinicians, engineers, and surgeons in academia and industry for the development and commercialization of cell therapies (Schmidt, 2008).

5.2. Implications for policy

The discussions of this section emphasized the multiple conduits through which the new therapeutic approaches based on stem cells have emerged. Some of these interactions may be more dominant than others, as observed by Petersen et al. (2016) in the strongest links between demand (disease) and technological capabilities (analytic, diagnostic, and therapeutic techniques) in their cases studies. We believe that the predominance of certain sets of interactions is highly dependent on the stage of technological development of therapy and the nature of the targeted disease. Throughout this study, we described how progress in cell therapies for AMD disease has advanced through multiple interactions among the understanding of disease, biomedical technologies, and pre-clinical procedures (Morlacchi and Nelson, 2011; Nelson et al., 2011; Petersen et al., 2016), as visually represented in Supplementary Information 2. Policy makers should be aware of the different types of interactions involved in the development of new therapies, as "global pictures" can provide an overview of their respective areas of influence and action.

Fostering and stimulating the variety of technological possibilities is crucial for the progress of emerging therapeutic technologies, as it is not known from which directions and in which ways potential treatments will emerge (Ávila-Robinson, 2013). New medical technologies involve long, uncertain, and resource-intensive research, development and translational efforts lasting 15 to 30 years to mature into safe and effective therapies, as seen in the cases of recombinant DNA technologies and monoclonal antibodies (NASEM, 2017; Rao et al., 2015). Once potential therapeutic approaches materialize, even as primitive proofs-of-concept, they can harness the accelerated accumulation of knowledge, which may spur the development of other improved therapeutic approaches. As described above, for complex diseases, such as AMD, policy makers should expect to see a "patchwork" of co-existing therapies, rather than a "holy grail" therapy, to tackle different disease stages, levels of severity, as well as genetic and environmental backgrounds. By fostering regulating frameworks enabling multiple technologies, policy makers could take advantage of functional and structural overlaps across technologies (Bergek et al., 2008).

Keeping in mind the regime-niche interactions described above, the future of emerging iPS cell-based therapies does not depend solely on their own merits but also on how well they cope with and exploit the incumbent therapies and complementary technologies. The understanding of such broader contexts of an emerging therapy is crucial to grasping their potential for development and diffusion (Kukk et al., 2015; Wirth and Markard, 2011). It is well known that policy can have a direct implication on fostering and nurturing the development of the emerging technologies, as seen in the literature of niche protection and "protective spaces" (Boon et al., 2014; Lopolito et al., 2011; Lopolito et al., 2013). For instance, system builders are highly influential in the introduction of an emerging technology into a modern healthcare landscape (Kukk et al., 2015); for example, in the exploitation of the current infrastructures or institutions, or their replacement. Representative examples are the redesign of Japan's regenerative medicine institutional landscape and the introduction of fast-track review processes that lead to breakthrough therapies in several countries (Azuma and Yamanaka, 2016; Sengoku et al., 2015).

These results highlighted the role of more subjective matters such as organ complexity and ease-of-experimentation in the development of emerging fields of medicine. Moreover, amid the uncertainty and ambiguity surrounding the evolution of emerging therapies, the field of iPS cell-based therapies appears to be evolving cautiously. Talks with researchers have pointed towards the need for such caution as clinical trials that

endanger human life can negatively influence the development of the whole field. This has already been attested in the field of gene therapy, which experienced a series of serious events. These were caused by the use of viruses as delivery methods for the gene to be corrected in patients, which resulted in the complete termination of gene therapy trials in the United States (Judson, 2006). In the case of AMD disease, this cautious progress is illustrated with the decision made by the research team to put a hold on the pioneering iPS cell pre-clinical trial after three mutations were discovered in the tissue prepared for the second patient (Garber, 2015).

Owing to the close coupling between product and process innovations, the evolution of new cell therapies should be accompanied with the early consideration of downstream activities, such as standardization, reimbursement approaches, and production scaling-up (Sengoku et al., 2011). In this regard, there is a need for policy makers to establish support programs fostering downstream activities at early stages of cell therapy development. Relatedly, policy makers should consider curiosity-driven research with an eye on potential therapeutic uses of emerging biomedical technologies (Yamanaka, 2013), as well as the need for tailored and targeted policies that take into account the characteristics of the disease, the targeted organs, and the nature of the therapies.

5.3. Limitations of this study

As with any research method, bibliometric-based approaches have inherent limitations and drawbacks. Throughout this study, we approached the complexity of the evolution of medical knowledge through the simplified and imperfect representations provided by bibliometric data. Although we attempted to circumvent these limitations by the simultaneous use of scientific, technological, and clinical trial data, we may have missed pieces of information either still undisclosed or not available in the different databases used in this study. Additionally, technological emergence involves several factors, including government initiatives and recent advances, which may not necessarily be reflected in bibliometric data. Despite their imperfect nature, however, these approaches embody reproducible, informed and evidence-based approximations of reality for the study of emerging technologies.

6. Concluding remarks

Our results highlighted the particularities of the emergence of new stem cell-based therapies, built on the case of iPS cell-based therapies for AMD disease. We contributed to the study of emerging technologies by revealing the factors influencing the evolution of cell therapy knowledge into clinical practices. We showed that cell therapy evolution is characterized by the significance of the diversity of technological possibilities, the role of subjective issues in the selection of directions of search, such as organ complexity and “experiment-ability,” the complementary nature between established and emerging therapies, and the tight product-process interdependencies. Our results also highlighted the high dependence of the evolution of therapies on the characteristics of the disease, the targeted organs, and the nature of the clinical procedure. Policy makers should be aware of these aspects, as they can be exploited to understand the difficulties facing emerging therapies and to find ways in which these can be circumvented to become effective and safe clinical practices.

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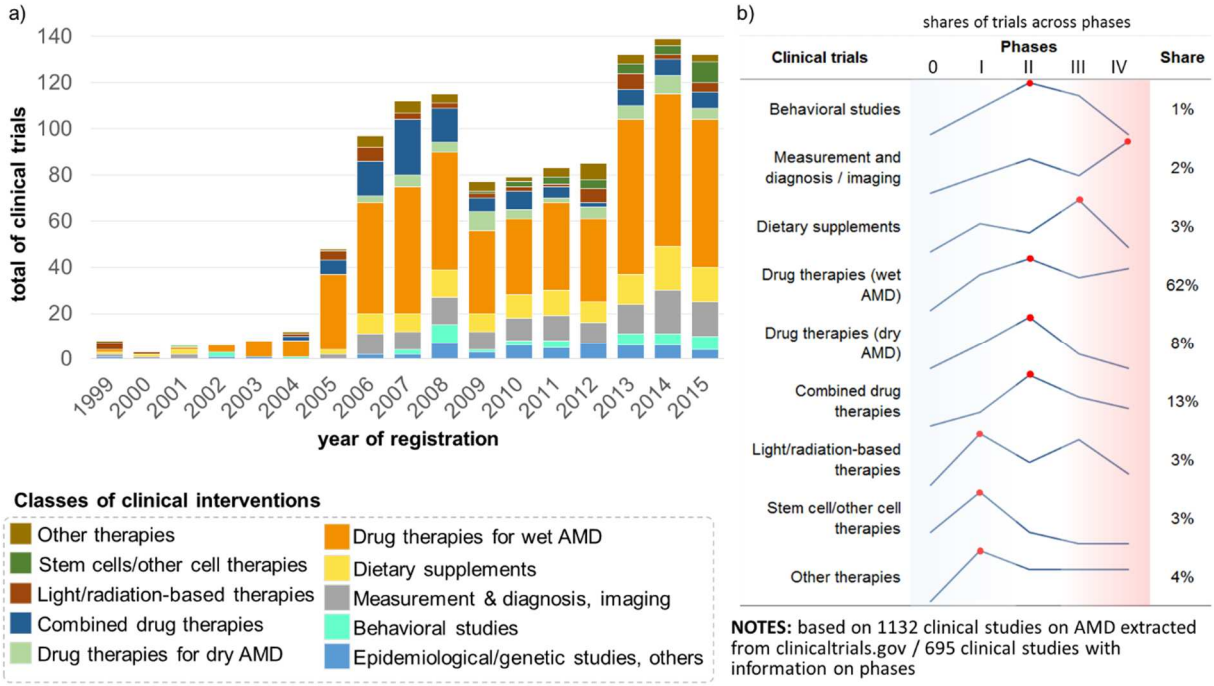
Supplementary Information 1 Clinical practices for AMD through clinical trials

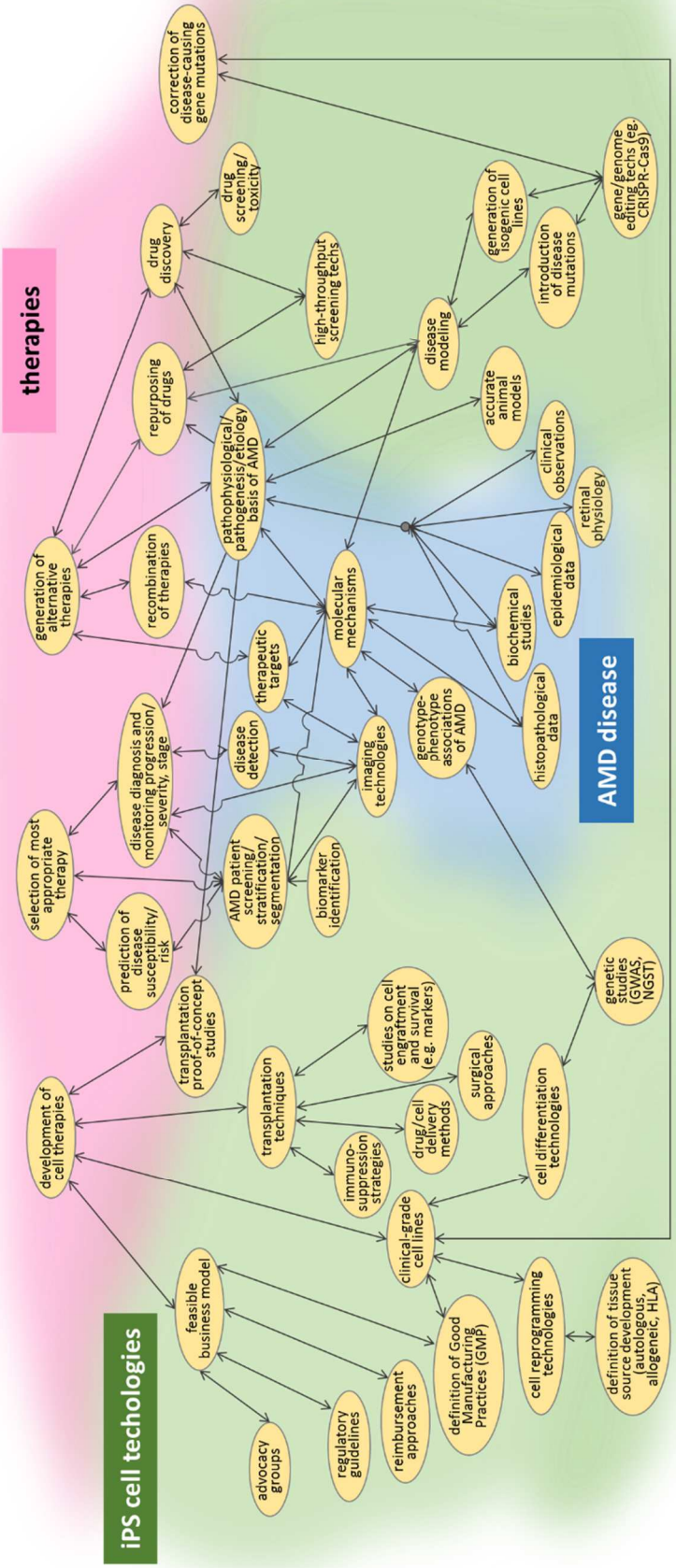
We collected clinical trial data to gain insights into the therapeutic landscape of AMD. Figure 8a illustrates the total of number of registered AMD clinical trials from the 1999 to 2015.



Longitudinal trends in the types of clinical interventions and b) shares of clinical trials by clinical phase

From Fig. 1a), we observe a clear dominance of drug-based approaches, particularly those for wet-AMD trailed by drugs for dry-AMD and therapies that combine multiple drugs and/or non-drug approaches. The in-take of dietary supplements, such as certain vitamins and minerals, appear highly influential because of their beneficial effects on the still incurable dry-AMD. Interestingly, clinical trials using cell-based therapeutic approaches have increased significantly in the year 2015. This may be attributable to their emerging nature; despite their growth, compared to drug-based approaches, the influence of cell-based approaches is still small. An analysis of the specific interventions examined in clinical trials shows that the therapeutic landscape is broad; for instance, we found over 100 and 30 drugs tested for wet- and dry-AMD, respectively. These drugs differ in their chemical classes, mechanisms of action, and methods of application. This is in line with the well-known strategy of testing and re-testing different therapeutic solutions common in emerging biomedical technologies. Fig. 1b) shows also that these therapies vary in terms of their maturity as inferred from the distribution of clinical trial phases, from 0 to IV. Based on these distributions, we see that stem cell therapies show the highest degree of emergence as they tend to be concentrated in the early phases of clinical development. In contrast, drugs for wet-AMD are spread over phases III and IV, as shown in Fig. 1b). The main driver behind the development of multiple therapeutic approaches appears to be the lack of curative methods. Drug-based approaches have dominated the therapeutic landscape but they are palliative in nature; in addition, they require frequent, highly invasive, expensive, and risk-prone intra-ocular injection procedures.

Supplementary Information 2 Mind map of interactions between basic science, biomedical technologies, and clinical practice



Interrelations among the three pathways of the Nelson's model. Connections between nodes relied on the collection of relevant issues extracted from the results of previous sections, talks with experts, and the evaluation of technical journals and reports. We arranged the network nodes according to their proximity to their connecting nodes.

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